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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ING10631PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/14834	International filing date *(day/month/year)* 23.12.2003	Priority date *(day/month/year)* 23.12.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/47		
Applicant INGENIUM PHARMACEUTICALS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.07.2004	21.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Steffen, P Telephone No. +49 89 2399-7307

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/14834

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-124 as originally filed

Sequence listings part of the description, Pages

1-12 as originally filed

Claims, Numbers

1-207 as originally filed

Drawings, Sheets

1/20-20/20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 36,41,45,49,69,71,73,104,105 (all partly); 184,187,190 (partly),191,206,207; 96-103, 172-182,184-186,190 (IA)

   because:

   ☒ the said international application, or the said claims Nos. 96-103, 172-182,184-186,190 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 36,41,45,49,69,71,73,104,105 (all partly); 184,187,190 (partly),191,206,207

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-44,49,54-68,70,72-103,127-134,154-182,187,197-199
	No:	Claims	45-48,50-53,69,71,104-126,135-153,183-186,188-190,192-196,200-205
Inventive step (IS)	Yes:	Claims	NONE

	No:	Claims	1- 44,45- 48,49, 50-53, 54-68, 69,70,71, 72-103, 104- 126, 127- 134, 135- 153, 154-182,183-186,187,188-190,192-196,197-199,200-205
Industrial applicability (IA)	Yes:	Claims	1-95,104-171,183,187-189,200-205
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No international search report has been established by the PCT/ISA for the subject-matter of claims 36, 41, 45, 49, 69, 71, 73, 104, 105 (partly); 184, 187, 190 (partly), 191, 206, 207. Consequently and according to rule 66.1(e) PCT no examination is carried out for that claimed subject-matter.

Claims 96-103 and 172-182, 184-186, 190 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 98/41627 A (ZYMOGENETICS INC) 24 September 1998 (1998-09-24)
Cloning of human gob-4 (hAG-2) called here zsig10. Expression of the gene in lung, prostate, small intestine, colon, trachea and stomach e.g. tissues that possess goblet cells. Role in correct mucous clearing, production, integrity and composition suggested. A link is made to obstructive pulmonary disease, inflammatory bowel disease and Crohn's disease, all diseases that the application also proposes to diagnostisise or cure. Only WT protein and gene, no mutant.

D2: WO 01/63290 A (BOYD ROBERT SIMON ;OXFORD GLYCOSCIENCES UK LTD (GB); STAMPS ALASDA) 30 August 2001 (2001-08-30)
Selective expression of hAG-2 in breast cancer. Mutants suggested.

D3: KOMIYA T ET AL: "Cloning of the gene gob-4, which is expressed in intestinal goblet cells in mice." BIOCHIMICA ET BIOPHYSICA ACTA. NETHERLANDS 19 MAR 1999, vol. 1444, no. 3, 19 March 1999 (1999-03-19), pages 434-438, ISSN: 0006-3002

Cloning of gob-4 from mouse, expression study. Shows that gene in selectively expressed in goblet cells (mucus secreting cells) in stomach, intestine and colon. Suggests a role for the protein encoded by gob-4 in mucus secreting function.

D4: THOMPSON D A ET AL: "HAG-2, THE HUMAN HOMOLOGUE OF THE XENOPUS LAEVIS CEMENT GLAND GENE XAG-2, IS COEXPRESSED WITH ESTROGEN RECEPTOR IN BREAST CANCER CELL LINES" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 251, no. 1, 9 October 1998 (1998-10-09), pages 111-116, XP001009725 ISSN: 0006-291X

Cloning of hAG-2 from mouse and human, expression study. Shows that gene in selectively expressed in tissues containing mucus secreting cells (stomach, intestine, colon, trachea). Shows also that hAG-2 is co-expressed with estrogen receptors in breast cancer cells. Makes also a link to mucus secretion.

The present application relates to the detection of a mutation in the mouse and corresponding human gene of gob-4 (= hAG-2) which is linked to altered goblet cell function e.g. impaired mucus production and in particular mucin secretion. The mutation leads to an amino acid exchange V->E in position 137. Transgenic mice carrying the mutation show disease syndromes associated with altered mucus production such as diarrhea and thriving deficit.

Claims are not all particularly relating to the mutant presented in the present application e.g. many cover also uses and methods employing the known WT protein hAG-2 (gob-4). However, from D1-D4 it is clear that in the art this gene and protein 1) had been linked to mucus secretion/integrity, 2) were specifically expressed in goblet cells which are mucus secreting cells. Vague claims of methods, uses and products (such as antibodies, siRNA etc.) directed to the WT protein are therefore largely suggested or even disclosed in the prior art. Also many of the diseases mentioned in the claims are already brought forward by D1 such as obstructive pulmonary disease, inflammatory bowel disease and Crohn's disease. Hence claims 45-48, 50-53, 69, 71, 104-126, 135-153, 183-186, 188-190, 192-196, 200-205, if yet novel aren't in any case considered to be built on inventive step, contrary to Article 33(3) PCT.

Likewise, with what was known for hAG-2 (gob-4) function e.g. expression in goblet cells,

implication in mucus production and disease, the vague delimitation of the mutants to conferring altered goblet cell function and/or increased risk of disease associated with goblet cell function appears not sufficient in order to establish an inventive step over the prior art which also do mention mutants of the gene and protein in question. This is the case for claim 1 and all similarly worded claims. Indeed the skilled artisan could imagine with the general knowledge any generic mutants of the gene that alter in any manner goblet cell function and/or mucus secretion (for example D1, page 62 -> search for mutants in connection with functional disclosure on pages 23-26). Likewise he would reasonably expect that mutations in said gene would cause disease related to altered goblet cell function.

Re Item VIII

Certain observations on the international application

Clarity, Article 6 PCT

The claims are manyfold and messy. In their ensemble they are therefore in breach with Article 6 and Rule 6 PCT.

Vague and interpretable statements such as in claim 1 and similarly worded ones (altered biological activity, increased risk of a disease associated with alteration in goblet cell function) render them contrary to Article 6 PCT, especially that these terms try to define the product itself.

Claims 104, 105, 135 and 137 are not describing methods for searching mutations in agr2 (hAG-2 or gob-4) but methods for finding markers that are indicative of and increased risk of alteration of goblet function by comparing differences between two samples, said difference being indicative of a mutation in agr2. In the absence of any indication to the (biological) nature of the differences (what are they and when are they indicative of the said mutation?) the skilled artisan should actually compare, these methods are thus completely unclearly defined. It is moreover not apparent how the skilled artisan could carry out such a method in the absence of the information in question, absence not only in the claims but also from the description.